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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION IX
75 Hawthorne Street
San Francisco, Ca. 94105

Dr. Yi Wang
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street; 16th Floor
Oakland, CA 94612

Attention: PHG Project - Perchlorate

Dear Dr. Wang,

Thank you for the opportunity for the United States Environmental Protection Agency (U.S. EPA) Region 9 Office to provide comments on the recently proposed Public Health Goal for perchlorate in drinking water. We applaud the initiative of the State of California in assessing the public health risks from this chemical that has so recently been identified as a potential threat to drinking water supplies.

Scientists from U.S. EPA's Office of Research and Development (ORD) published a draft toxicity assessment for perchlorate in January, 2002. An external peer review of U.S. EPA's draft toxicity assessment for perchlorate was conducted on March 5 and 6 in Sacramento, a location selected to allow State of California staff direct access to the scientific discussions. U.S. EPA ORD scientists have provided extensive detailed comments on the State of California's draft report.

Our regional office is enclosing comments emphasizing several important limitations of human clinical studies which the State of California relied on in development of the draft PHG. We would recommend increasing the total uncertainty factor or other modifying factors to ensure that the PHG is appropriately protective. We also include comments from our Office of Research and Development with regard to the use of data on accumulation of perchlorate in lettuce.

It is gratifying that the State of California has independently derived a Public Health Goal that so closely approximates the result of EPA's analysis. If the State were to conservatively account for the uncertainties inherent in the use of the human clinical studies, the two assessments would be essentially identical.

We look forward to continuing to work with you to better understand the impact of perchlorate on human health and environment. If you have any questions regarding this letter, please feel free to contact Kevin Mayer, Region 9 Perchlorate Coordinator at (415) 972-3176.

Sincerely

Alexis Strauss 25 April 2002

Alexis Strauss
Director, Water Division

Comments on State of California's Draft Public Health Goal for Perchlorate
U.S. Environmental Protection Agency, Region 9
April 25, 2002

Use of human data

Two human clinical research efforts (Lawrence et al. and Greer et al.) form the basis of the State of California's PHG assessment. The clinical study of Greer et al. was originally designed to provide information on the disposition of perchlorate in humans to support development of a physiologically based pharmacokinetic model to allow a quantitative interspecies extrapolation. In reviewing the Quality Assurance/Quality Control report (Merrill, 2001) from the Lawrence et al. studies, the U.S. Department of Defense found serious deficiencies that precluded the use of these data for the model development. Similar reservations in relying on the Lawrence et al. data to calculate a level protective of public health would seem prudent

The State of California and U.S. EPA both agree that none of the human clinical studies provide adequate information on the potential effects on sensitive subpopulations, particularly for developing infants and for people with compromised thyroids. Data from animal studies confirm that perchlorate is of particular concern for neurodevelopmental effects in these populations. These data and the literature on iodide deficiency supports the concern that hypothyroxinemia alone (decreased thyroid hormone without compensatory increases in Thyroid Stimulating Hormone (TSH)) is of concern in these populations. The limited number of healthy adult volunteers subjected to each perchlorate dose in the clinical studies further reduces confidence in our ability to adequately account for variability of the effects of perchlorate within human populations. For example, in the Greer et al. study there were only seven subjects at the lowest dose level, a sample size insufficient to detect an effect. We would concur that at least a full uncertainty factor of 10 or other modifying factor for study deficiencies must be used to account for this critical information gap if the PHG is to be based on the human clinical studies.

Based on their review of the recent manuscript, EPA's recent external peer panel was quite clear that the Greer et al. study did not establish a "No Observed Adverse Effect Level". The panel emphasized that healthy adult humans store thyroid hormones sufficient to supply several week's requirements even after blockage of the iodide uptake mechanism in the thyroid. The degree of thyroid hormone deficiency that is adverse in a population is a topic of considerable controversy. Recent epidemiological data have called clinical norms into question, especially for pregnant women and their children. In light of those uncertainties, it is difficult to assert that the degree of iodide inhibition is a LOAEL, especially when integrated with the laboratory animal evidence. Further, both statisticians on the panel suggested additional analyses rather than a log transform that makes extrapolation to the origin impossible and linearizes the low-dose effects. Absent a true "No Observed Effect" measurement in a scientifically valid study, we recommend an additional uncertainty factor to account for this lack of critical information.

Since the State of California's draft relies on human clinical studies which dosed the volunteer subjects for only two weeks, considerable uncertainty remains regarding chronic toxic effects over a lifetime. Even the animal studies that are available have not fully satisfied this issue,

resulting in U.S. EPA's use of an uncertainty factor of 3 (half of an order of magnitude) for incomplete information on long-term exposures. The external peer review panel endorsed the notion of *in utero* programming and echoed the concern that long-term low-level exposures may result in a reset of the feedback control regulating thyroid hormeostasis. The genetic toxicology expert noted that this type of finding was common for non-mutagenic carcinogens. Thus, as in many cases of groundwater contamination by recalcitrant chemicals, low-level exposure to perchlorate could occur over full lifetimes or even generations. We recommend that a full order of magnitude uncertainty factor or other modifying factor for duration of effects should be employed if short-term dose human studies form the basis of the State's assessment.

Use of lettuce data

We are also concerned about the interpretation of data in the sections on Drinking Water, Environmental Occurrence and Human Exposure, Food (pp. 13-14) and Calculation of the Public Health Goal (pp. 76-78). Both sections cite EPA 2001 as the source of information, which in turn cites the work of Hutchinson and co-workers and a 2000 presentation at the Battelle chlorinated solvents conference in Monterey, CA. We note that the authors of EPA 2001 draft Chapter 10 Evaluation of Evidence for Indirect Exposure, Collette and Urbansky, had Hutchinson review a draft of that paragraph, who made some changes.

Both Chapter 10 and pp. 13-14 of the CA EPA draft acknowledge that results presented at Monterey (Hutchinson et al. 2000) and those supplied by Hutchinson cannot be directly extrapolated to "edible agricultural produce." Yet, CA EPA proceeded to do so on p. 78 of the draft. The basic information that 10 mg perchlorate/L exposure to lettuce in about 50 days leads to 300 ug/g perchlorate accumulation in lettuce is somewhat correct (behavior of the data are not accurately described in EPA 2001 in all aspects and the data do not support some of the speculation in the draft). However, there are also data for exposures of lettuce down to 10 ppb perchlorate that show an order of magnitude less accumulation. These data are undergoing final QA analysis for publication in the near future. More importantly for the use of the data are the experimental conditions involved. Lettuce was grown in washed sand and irrigated with solutions of sodium perchlorate. The sand does not represent soils that may be high in salt. The solution did not contain important competitive ions, especially nitrate, sulfate, chloride, and others that we know to be important in the uptake, accumulation and degradation of perchlorate from our studies and studies we have commissioned on the phytoremediation of perchlorate (Susarla et al. 1999, 2000; Nzengung et al. 2000). Further, we do not think that the washed sand initially represented microbial communities of the rhizosphere. In hydroponic studies of willow and other trees we have supported (Nzengung et al. 2000), rhizodegradation has been observed to start in 20 to 30 days. However, we expect rhizodegradation to be ongoing in soil with sufficient organic carbon and other constituents, with very little lag if any after planting. Any rhizodegradation would prevent some accumulation. We recommend that extrapolations of these data to estimate possible human exposures be redone to reflect more realistic values.